

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. § 371

09/646355 ✓

U.S. APPLICATION NO. (If known, see 37 C.F.R. § 1.5): \_\_\_\_\_

INTERNATIONAL APPLICATION NO.

PCT/EP99/01374 ✓

INTERNATIONAL FILING DATE

3 March 1999 ✓

PRIORITY DATE CLAIMED

18 March 1998 ✓

## TITLE OF INVENTION:

DRUG FOR THE PROPHYLAXIS AND/OR TREATMENT OF BREAST CANCER, COMPRISING A STEROIDAL  
AROMATASE INHIBITOR

APPLICANT(S) FOR DO/EO/US: Alfred SCHMIDT et al. ✓

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

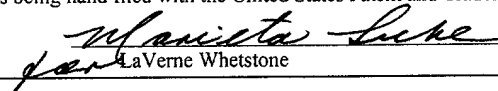
1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. § 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. § 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. § 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. § 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. § 371(c)(2))
  - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. § 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. § 371(c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. § 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. § 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. § 371(c)(5)).

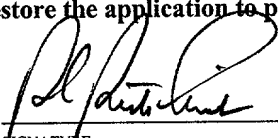
## Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§ 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.  
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: 1. Various PCT documents 2. Return receipt postcard.

## CERTIFICATE OF HAND DELIVERY

I hereby certify that this correspondence is being hand filed with the United States Patent and Trademark Office in Washington, D.C. on September 18, 2000.

  
 LaVerne Whetstone

|  |              |   |           |
|--|--------------|---|-----------|
| U.S. APPLICATION NO. <b>09/646355</b><br>INTERNATIONAL APPLICATION NO. PCT/EP99/01374  |              | DOCKET NUMBER: 246472001600                       |           |
| 17. <input checked="" type="checkbox"/> The following fees are submitted:<br><b>BASIC NATIONAL FEE (37 C.F.R. §§ 1.492(a)(1)-(5)):</b><br>Neither international preliminary examination fee (37 CFR 1.482)<br>nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO<br>and International Search Report not prepared by the EPO or JPO ..... \$840.00<br>International preliminary examination fee (37 CFR 1.482) not paid to<br>USPTO but International Search Report prepared by the EPO or JPO ..... \$670.00<br>International preliminary examination fee (37 CFR 1.482) not paid to USPTO<br>by international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$690.00<br>International preliminary examination fee paid to USPTO (37 CFR 1.482)<br>but all claims did not satisfy provision of PCT Article 33(1)-(4) ..... \$970.00<br>International preliminary examination fee paid to USPTO (37 CFR 1.482)<br>and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$96.00 |              | <b>CALCULATIONS PTO<br/>USE ONLY</b>              |           |
| <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>  |              | \$690.00  |           |
| Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from<br>the earliest claimed priority date (37 C.F.R. § 1.492(e)).   |              | \$0   |           |
| CLAIMS   | NUMBER FILED | NUMBER EXTRA                                      | RATE      |
| Total claims   | 13 - 20 =    | 0   | x \$18.00 |
| Independent claims   | 1 - 3 =      | 0   | x \$78.00 |
|  |              | + \$260.00  | \$260.00  |
| <b>TOTAL OF ABOVE CALCULATIONS =</b>   |              | \$950.00  |           |
| Reduction by ½ for filing by small entity, if applicable. Verified Small Entity Statement must<br>also be filed (Note 37 C.F.R. §§ 1.9, 1.27, 1.28)  |              | \$0   |           |
| <b>SUBTOTAL =</b>  |              | \$950.00  |           |
| Processing fee of <b>\$130.00</b> for furnishing the English translation later than<br><input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 C.F.R. § 1.492(f)).  |              | \$0   |           |
| <b>TOTAL NATIONAL FEE =</b>  |              | \$950.00  |           |
| Fee for recording the enclosed assignment (37 C.F.R. § 1.21(h)). The assignment must be<br>accompanied by an appropriate cover sheet (37 C.F.R. §§ 3.28, 3.31). <b>\$40.00 per property</b>  |              | \$0   |           |
| <b>TOTAL FEES ENCLOSED =</b>   |              | \$950.00  |           |
|  |              | <b>Amount<br/>to be<br/>refunded:</b>             | \$        |
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| a. <input checked="" type="checkbox"/> A check in the amount of \$950.00 to cover the above fees is enclosed.<br>b. <input checked="" type="checkbox"/> The Assistant Commissioner is hereby authorized to charge any additional fees that may be required, or credit any<br>overpayment to <b>Deposit Account No. 03-1952</b> .<br><br><b>NOTE: Where an appropriate time limit under 37 C.F.R. § 1.494 or 1.495 has not been met, a petition to revive<br/>         (37 C.F.R. § 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b><br><br>SEND ALL CORRESPONDENCE TO:<br><br>Barry E. Bretschneider<br>Morrison & Foerster LLP<br>2000 Pennsylvania Avenue, N.W.<br>Washington, D.C. 20006-1888   |              |   |           |
| <br>SIGNATURE  |              | Barry E. Bretschneider<br>Registration No. 28,055 |           |

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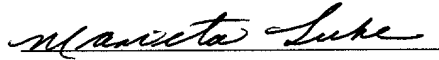
534 Rec'd PCT/PTO 18 SEP 2000

PATENT

Docket No. 246472001600

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for LaVerne Whetstone

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Alfred SCHMIDT et al.

Serial No.: Not yet Assigned

Filing Date: September 18, 2000

For: DRUG FOR THE PROPHYLAXIS  
AND/OR TREATMENT OF BREAST  
CANCER, COMPRISING A  
STEROIDAL AROMATASE  
INHIBITOR

Examiner: Not yet Assigned

Group Art Unit: Not yet Assigned

PRELIMINARY AMENDMENT

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Prior to the calculation of the filing fee for this application, as part of this original application filing, please enter the following amendment:

IN THE SPECIFICATION

Page 9, line 14, change "hydrophilicity" to --hydrophobicity--.

### REMARKS

The amendment to the specification above corrects an obvious error in the original German-language text of the international application as translated into English in the text filed with this application. Persons skilled in the art would recognize that this error is obvious from the discussion starting at page 4, line 21, of the application as filed herewith, which refers to the lipophilicity and hydrophobicity of the active compound used in accordance with this invention, which is, as can readily be gleaned from the specification as filed, the acetylated formestane referred to at page 9, lines 13-15.

Early action entering this amendment and allowing the claims in this application is solicited.

In the event that the transmittal letter is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 18, 2000

Respectfully submitted,

By: 

Barry E. Bretschneider  
Reg. No. 28,055

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APPLICANT or PATENTEE:

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## [ ] FOR INDEPENDENT INVENTOR(S)

As a below-named inventor, I hereby declare that I am an independent inventor who (1) has not assigned, granted, conveyed, or licensed, and (2) is under no obligation under contract or law, to assign, grant, convey, or license, any rights in the invention, to any person who could not likewise be classified as an independent inventor if that person had made the invention, or to any concern which would not qualify as a small business concern or a nonprofit organization, as defined in 37 CFR 1.9.

## [X] FOR SMALL BUSINESS CONCERN

I hereby declare that S.W. Patentverwertungs GmbH is a business concern which qualifies as a small business concern as defined in §1.9(d) - namely, (1) whose number of employees, including those of its affiliates, does not exceed 500 persons; and (2) which has not assigned, granted, conveyed, or licensed, and is under no obligation under contract or law to assign, grant, convey, or license, any rights in the invention to any person who could not be classified as an independent inventor if that person had made the invention, or to any concern which would not qualify as a small business concern or a nonprofit organization under this section; and that the exclusive rights to the invention have been conveyed to and remain with the above-identified small business concern.

I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful, false statements and the like, so made, are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the patent application or any patent issuing thereon.

Each of the undersigned hereby grants the firm of Morrison & Foerster, LLP  
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## INVENTOR(S)

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Date: Nov. 15, 2000

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Date: Nov. 15, 2000

Name:  
Date:

Name:  
Date:

## SMALL BUSINESS CONCERN:

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Name: S.W. Patentverw.

Title: GmbH

Date: Nov. 15, 2000

By: B. Wieland

Name: \_\_\_\_\_

Title: \_\_\_\_\_

Date: 11.15.00

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PCT/EP99/01374

WO 99/47143

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**DRUG FOR THE PROPHYLAXIS AND/OR TREATMENT OF BREAST CANCER,  
COMPRISING A STEROIDAL AROMATASE INHIBITOR**

10

The invention relates to a medicament for the prophylaxis (primary and secondary prophylaxis) and/or treatment of breast cancer.

15

Breast cancer is the most frequent malignant disease in women. In Germany, breast cancer makes up about 20% of all cases of cancer in women; the incidence at present is about 30,000 new cases of disease per annum. The adjuvant cancer therapy used today does lead to an increase in the survival rate; breast cancer screening and early surgical treatment can also lower the mortality by over 30%. However, since the number of new cases of disease is continuously increasing, the death rate measured over the total population remains the same or increases. Until now, it has barely been possible to affect the number of new cases, as too little is known about triggering factors.

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In approximately half of all breast cancers, oestrogen and/or progesterone receptors are found in the cytoplasm. Breast cancers of this type need oestrogen for the proliferation of their cells. Oestrogens act by binding to specific intracellular (cytoplasmic) receptors of oestrogen-sensitive cells, into which they are passively introduced by diffusion from the plasma. The binding changes the configuration of the re-

ceptor protein. The receptor-hormone complex controls both the transcription and the expression of specific genes; the synthesis of growth-promoting and/or growth-inhibiting factors caused thereby finally has an effect on cell growth.

5

By withdrawal of oestrogens, regression of oestrogen-dependent tumours can be achieved. In premenopausal women, the ovaries are the main source of oestrogens. Their surgical removal has therefore been carried out since 1896 with breast cancer in the advanced stage (metastasis formation) as a so-called surgical hormone therapy.

10

In post-menopausal women, the conversion of adrenal androgens, especially androstenedione and testosterone, to oestrone and oestradiol is the main source of oestrogen. The conversion to oestrogens takes place in the muscle and fatty tissue.

15

In clinical practice, for over twenty years both early and advanced stages of breast cancer have been treated with tamoxifen or its derivatives (in particular tamoxifen citrate). Tamoxifen occupies the oestrogen receptors located in the cytoplasm of the cancer cells and thus causes competitive displacement of oestrogens. The complex formed from tamoxifen and the oestrogen receptor prevents the transcription and the expression of genes promoting cell growth, which otherwise is caused by a complex formed from oestrogens and the receptor.

20

25

In in-vitro experiments, it has been demonstrated that tamoxifen also has a growth-inhibiting and, under certain circumstances, even cytostatic effect on cell lines which have no oestrogen receptors. Tamoxifen inhibits protein kinase C

30

and blocks the activation of calmodulin. It increases the activity of the killer cells and inhibits suppressor T lymphocytes.

5 In particular after relatively long treatment, tamoxifen can act on cancer cells as well as oestrogens in a manner which is not known in greater detail and promotes their growth. Relatively long-lasting tamoxifen treatment can therefore lead, under certain circumstances, to tumour growth. It  
10 moreover leads to a risk which is increased by a factor of 3 to 5 of suffering from cancer of the endometrium. In view of the clinical benefits of tamoxifen therapy, this risk is accepted in breast cancer patients.

15 The systemic treatment of breast cancers with aromatase inhibitors, in particular 4-hydroxyandrost-4-ene-3,17-dione (INN formestane) is further known. Aromatase is a complex enzyme system which catalyses the conversion of adrenal androgens to oestrone and oestradiol.

20 Formestane is a derivative of the physiological steroid hormone androstenedione and binds competitively to other substrates of aromatase. During catalysis, it damages the enzyme molecule irreversibly. Systemic treatment with formestane is  
25 likewise used as an antioestrogenic breast cancer therapy.

The invention is based on the object of creating a medicament of the type mentioned at the outset, which is suitable for treatment, and in particular also prophylaxis, of breast cancer.  
30

The invention achieves this object by formulating a steroidal aromatase inhibitor to give a medicament intended for topical



application. The use of antigestagens as an additional constituent of the medicament is excluded in the context of the invention.

- 5 Some terms used in the context of the invention will first be explained.

According to the invention, steroidal aromatase inhibitors are used as substances inhibiting the formation of oestrogens. These inhibit oestrogen biosynthesis from the androgenic precursors, for example the enzymatic conversion of androstenedione to oestrone or of testosterone to oestradiol. Since the two synthesis steps mentioned are mediated by the enzyme system of the aromatase (converting enzyme), aromatase inhibitors are used in the context of the invention. Preferred inhibitors are those which bind to the aromatase and irreversibly damage this. After topical application, they penetrate through the skin and concentrate in the fatty tissue.

20 The medicament according to the invention is intended for topical application. The medicament is applied locally to the skin, the preferably strongly lipophilic active compound is transdermally absorbed and thus brought locally to the intended site of action. The active compound concentrates in the periductal fatty tissue. In a long-term treatment, the fatty matter of the treated breast is markedly reduced. This reduction decreases the quantity of oestrogen-forming cells having oestrogen-forming competence. The lipophilicity and hydrophobicity of the active compound has the result that the active compound is exclusively concentrated locally in the fatty tissue and can display no systemic action. Oestrogens

are understood as meaning all female sex hormones having an action comparable, for example, to that of oestrone and oestradiol.

5 In the use of aromatase inhibitors known from the prior art, such as formestane, it is intended to transport these to the site of action via the blood circulation. High serum concentrations of the aromatase inhibitor are aimed at, which, in addition to the desired action in the tumour, can lead to  
10 systemic side effects. In view of the severity of the illness, such side effects are accepted in acute therapy in view of the success desired. However, this does not come into consideration in the case of a preventive treatment against a still unexisting or clearly detected disease.

15 According to the invention, however, it is intended to apply the medicament topically immediately on or in the vicinity of the intended site of action. Unlike the prior art, no transport via the blood circulation to the intended site of action  
20 is aimed at. According to the invention, the result achieved is an adequate local active compound level in the tissue at risk (in prophylaxis) or in the diseased tissue (in therapy) without a noticeable absorption of the active compound taking place in the blood circulation. The crux of the invention is  
25 thus not only in the topical application per se, but in the local topical application in such a way that the active compound concentrates immediately in the tissue at risk and/or diseased tissue, and not indirectly via the blood circulation.

30 If metastasizing carcinomas are also to be treated and/or prophylaxis is to be carried out against these, the medica-

ment according to the invention can be applied topically to the intended site of action in such an amount that a noticeable absorption in the blood circulation additionally takes place and a serum level thus builds up which also transports the active compound to metastases. In this use too, a local absorption on or in the vicinity of the intended site of action also primarily takes place.

The medicament can be used for the treatment of breast cancer. After surgical primary care and, if appropriate, appropriate adjuvant therapy, this treatment can replace and/or supplement the hitherto customary systemic antioestrogenic therapy.

An important advantage of the invention is the possibility of also using the medicament for breast cancer prophylaxis. A particularly advantageous possibility of employment is so-called secondary prophylaxis. In female patients in whom a breast cancer is already present, there is a particularly high risk of a further carcinoma in the contralateral breast. The contralateral breast can then be treated prophylactically with the medicament according to the invention. A secondary prophylactic treatment of the diseased breast to avoid local recurrences is likewise possible.

In the case of so-called high-risk women, primary prophylaxis can be performed. The selection criteria which can be used for such a high-risk group are, for example, the facts that at least one female relative of first degree on the mother's side is or has been suffering from breast cancer on one side before the 45th year of life or bilaterally, or that on the mother's side at least one female relative of first degree

and an additional female relative are or have been suffering from breast cancer. Since the local application according to the invention virtually completely avoids possible systemic side effects of the active compound on account of its hydrophobicity, the indication for primary prophylaxis can be made relatively generously already in the presence of tissue having a comparatively low or average risk (for example histological finding Prechtel II or III). Prophylaxis can be started even if the conventional early diagnosis (palpation finding) is still negative, since this customary early diagnosis is inadequate and as a rule only detects a breast cancer when a systemic disease which is barely still curable is already present.

The medicament according to the invention is preferably applied locally and topically over a relatively long period of time (if needed up to lifelong) and application is carried out, for example, once or twice per day.

The active substances are selected from the group consisting of the (preferably lipid-soluble) steroidal aromatase inhibitors. On topical application, these lipid-soluble substances penetrate into the fatty tissue and locally prevent the de novo formation of oestrogens from the oestrogen precursors.

25

For example, steroidal aromatase inhibitors such as

4-hydroxyandrost-4-ene-3,17-dione (formestane),

6-methyleneandrosta-1,4-diene-3,17-dione (exemestane),

10 -(2-propynyl)estr-4-ene-3,17-dione (MDL 18962) and

30 7- $\alpha$ -substituted androstenedione derivatives can be used.

The names mentioned in brackets are the INNs (International nonproprietary names). For the terminology and structure of the substances mentioned, reference is likewise made to the "Rote Liste" and Römpp's chemical encyclopaedia.

5

Until now, the substances mentioned have only been used for the systemic therapy of breast cancer. According to the invention, however, the active compound is brought to the intended site of application by local application. When using  
10 aromatase inhibitors, the invention achieves a reduction of the aromatase activity in the fatty tissue of the breast, i.e. exactly in the position in which a tumour can be formed or grow. On relatively long-term use, the fatty matter of the breast and thus the amount of possible risk tissue is re-  
15 duced. Since breast cancers are frequently formed in upper breast quadrants of increased aromatase activity, particularly effective prophylaxis is possible there according to the invention.

20 The use according to the invention of aromatase inhibitors can be employed prophylactically or therapeutically even against those tumours of the breast which are themselves able to produce oestrogen or autocrine/paracrine stimulation. A lowering of the oestrogen concentration in the plasma barely  
25 has an effect on such tumours, but the reduction of the intratumoral aromatase concentration to be achieved according to the invention can affect such tumours on account of the use of cell-permeable inhibitors.

30 Since the active compounds administered according to the invention remain localized in the fatty tissue of the breast and display their intended action there on account of their

lipid solubility, the side effects induced by systemic application are eliminated. This reduction or exclusion of side effects allows significantly wider prophylactic use. The medicament according to the invention can be applied by patients themselves and frequent visits to the doctor for this purpose are not necessary.

A medicament formulated according to the invention preferably contains formestane.

10

Formestane derivatives such as, for example, acetylated formestane (for example 4-O-acetylandrost-4-ene-3,17-dione) are likewise preferably utilizable. The acetylation of the formestane increases its hydrophilicity and thus skin penetration significantly. Since the acetyl group is hydrolysed under the conditions prevailing in the subcutaneous region after passage through the skin, the actual active compound formestane is formed again in situ. When using such an acetylated formestane, a precursor of the actual active compound penetrating better through the skin is thus applied and the inventors have recognized that the actual active compound is formed in situ subcutaneously from this precursor.

As a rule, the active compounds used according to the invention are lipid-soluble and highly suitable for topical application. As already described above, the concentration in the fatty tissue of the breast avoids systemic side effects. To improve the skin penetration, substances known in the prior art which promote this can be added to the medicament according to the invention, for example hyaluronidases or DMSO (dimethyl sulphoxide).

The medicament is preferably formulated as an ointment, cream, gel, emulsion or lotion. Formulation as a powder or oil is also conceivable. Formulation bases are familiar to the person skilled in the art from the cosmetic and pharmaceutical industry and do not need to be explained here in greater detail. For example, vegetable oils and fats such as almond oil, peanut oil, olive oil, peach kernel oil, castor oil, plant extracts, ethereal oils; furthermore vegetable waxes and synthetic and animal oils, fats or waxes; lecithin, lanolin alcohols, carotene, fragrances, mono- or polyhydric alcohols, urea, preservatives and colourants etc. can be used. Formulation as an oil-in-water or water-in-oil emulsion is preferred.

The active compound content of the medicament (the content of substances inhibiting the formation of oestrogens) can be between 0.0001 and 20% by weight, preferably 0.6 and 10% by weight, further preferably 1 and 5% by weight. A customary range is 0.6 to 2% by weight.

If substances are admixed to promote skin penetration absorption, their content, when using hyaluronidases, can be, for example, between 0.01 and 1% by weight, preferably 0.05 and 0.2% by weight; when using DMSO between 1 and 25% by weight, preferably 5 and 10% by weight.

Embodiments of the invention are described below. In the drawing:

Fig. 1 shows the cytological result of a fatty cell aspirate before use of the medicament according to the invention,

- 5 Fig. 2 shows the corresponding result after daily use over the course of 3 months.

#### Example 1

- 10 The following constituents were mixed to give a cream:

|                                |       |
|--------------------------------|-------|
| Urea                           | 10 g  |
| Titanium oxide                 | 15 g  |
| Crude petroleum jelly          | 20 g  |
| Isopropyl palmitate            | 10 g  |
| Hardened peanut oil            | 10 g  |
| Tween 80                       | 5 g   |
| Formestane                     | 1 g   |
| made up with purified water to | 100 g |

#### Example 2

- 15 A gel was prepared from the following constituents:

|                             |        |
|-----------------------------|--------|
| Ethanol 90%                 | 7.0 g  |
| Carbopol <sup>®</sup> 934 P | 7.0 g  |
| Triethanolamine             | 2 g    |
| Polysorbate 80              | 5.0 g  |
| Glycerol                    | 3.0 g  |
| Formestane                  | 0.75 g |
| purified water to           | 100 g  |



## Example 3

A cream was prepared from the following constituents:

5

|                       |        |
|-----------------------|--------|
| Propylene glycol      | 25.0 g |
| Isopropyl myristate   | 6.0 g  |
| Sorbitan monostearate | 1.0 g  |
| Polysorbate 80        | 2.0 g  |
| Cetylstearyl alcohol  | 6.0 g  |
| Stearyl alcohol       | 2.0 g  |
| Glycerol monostearate | 1.0 g  |
| Hyaluronic acid       | 0.1 g  |
| Formestane            | 1.5 g  |
| purified water to     | 100 g  |

## Example 4

10 A cream was prepared from the following constituents. The constituents are indicated in this example by their INCI names.

## INCI

|                               |        |
|-------------------------------|--------|
| Ceteareth-25                  | 3.0 g  |
| PEG-4-polyglyceryl 2-stearate | 2.0 g  |
| Cetearyl alcohol              | 4.9 g  |
| Petrolatum                    | 10.0 g |
| Paraffinum perliquidum        | 3.0 g  |
| Sodium carbomer 400           | 0.14 g |
| Lactic acid                   | 0.02 g |
| Paraffinum perliquidum        | 2.0 g  |

13

|  |        |
|--|--------|
| Phenoxyethanol, dehydroacetic acid, benzoic acid | 0.4 g  |
| Perfume  | 0.08 g |
| Formestane                                       | 1.5 g  |
| made up with water to                            | 100 g  |

The mixture of phenoxyethanol, dehydroacetic acid and benzoic acid mentioned in the formulation is obtainable from Schülke & Mayr under the name Euxyl<sup>®</sup> K702.

5

## Example 5

A cream was prepared from the following constituents, which are indicated by their INCI names.

10

## INCI

|   |        |
|---|--------|
| Ceteareth-25  | 3.0 g  |
| PEG-4-polyglyceryl 2-stearate                               | 2.0 g  |
| Cetearyl alcohol  | 4.9 g  |
| Petrolatum  | 10.0 g |
| Paraffinum perliquidum                                      | 3.0 g  |
| Sodium carbomer 400   | 0.14 g |
| Lactic acid   | 0.02 g |
| Paraffinum perliquidum                                      | 2.0 g  |
| Phenoxyethanol, dehydroacetic acid, benzoic acid            | 0.4 g  |
| Perfume   | 0.08 g |
| 4-acetylandrost-4-ene-3,17-dione<br>(acetylated formestane) | 1.5 g  |
| made up with water to                                       | 100 g  |

## Example 6-

A clinical test of the recipe according to Example 1 was carried out. The findings of oversize breasts and medium-grade mastopathy were present in the 25-year-old volunteer.

A fine needle aspirate of the fatty tissue (0.6 mm puncture needle, fixation in absolute ethanol, staining: May-Grünwald-Giemsa) was withdrawn (Fig. 1). Distended fat cells and eccentric cell nuclei as a result of a high oestrogen influx are detected.

The volunteer then applied the cream according to Example 1 twice daily over a period of 3 months. Fig. 2 shows the fatty tissue aspirate after this use. A reduction in volume of the fatty tissue ("shrivelled" fat cells in a regular arrangement) and an increase in connective tissue is detected due to the aromatase inhibition. The results showed a reduction of the tissue at risk by about 50% and a distinct firming of connective tissue and skin.

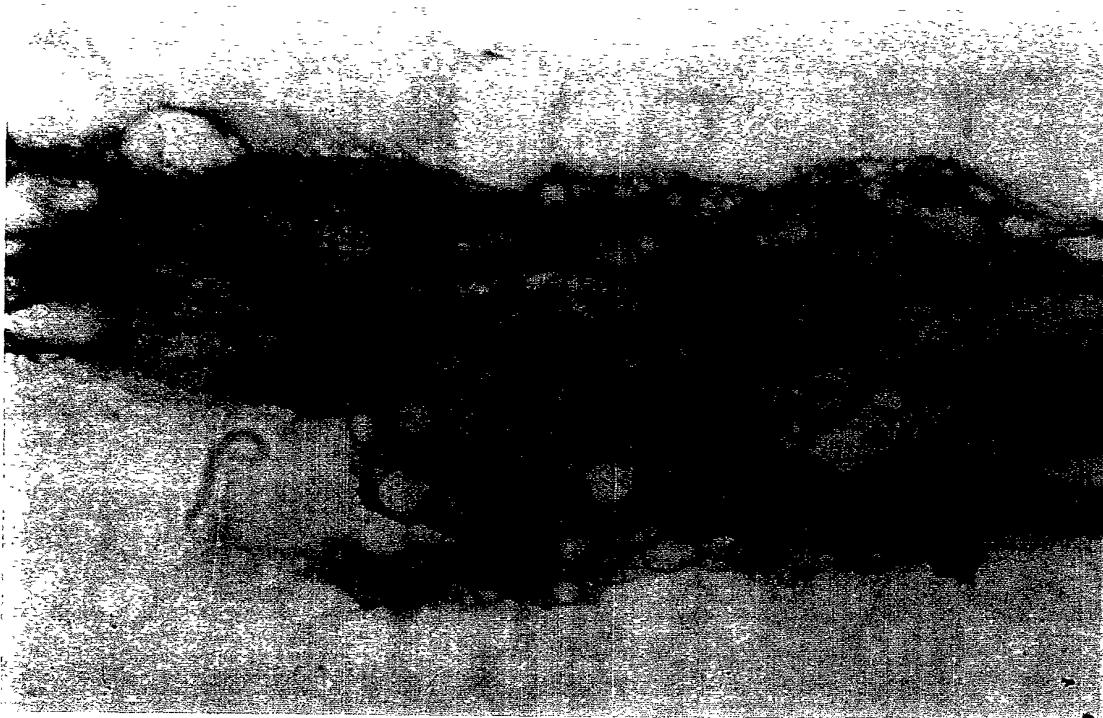
## Patent Claims

- 5     1.    Use of a steroidal aromatase inhibitor for the preparation of a medicament formulated for topical application for the prophylaxis and/or treatment of breast cancer, where the medicament contains no antigestagens.
- 10    2.    Use according to Claim 1, characterized in that the medicament contains formestane (4-hydroxyandrost-4-ene-3,17-dione) and/or a pharmacologically active formestane derivative.
- 15    3.    Use according to Claim 2, characterized in that the medicament contains 4-O-acetylandrost-4-ene-3,17-dione.
- 20    4.    Use according to one of Claims 1 to 3, characterized in that the medicament additionally contains substances for promoting skin penetration.
- 25    5.    Use according to Claim 4, characterized in that the medicament contains DMSO.
- 30    6.    Use according to one of Claims 1 to 5, characterized in that the medicament is formulated as an ointment, cream, gel, emulsion or lotion.
7.    Use according to Claim 6, characterized in that the active compound content is 0.0001-20% by weight, preferably 0.6-10% by weight, further preferably 1-5% by weight.

Fig. 1



Fig. 2



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TO 2720#9999215#011 P.06/08

PATENT  
Docket No.

### DECLARATION FOR UTILITY PATENT APPLICATION

AS A BELOW-NAMED INVENTOR, WE HEREBY DECLARE THAT:

My residence, post office address, and citizenship are as stated below next to my name.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

DRUG FOR THE PROPHYLAXIS AND/OR TREATMENT OF BREAST CANCER,  
COMPRISING A STEROIDAL AROMATASE INHIBITOR

the specification of which is attached hereto unless the following box is checked:

- ☒ was filed on September 18, 2000 as United States Application Serial No. 09/646,355 ✓
- ☒ as amended by the Preliminary Amendment filed concurrently with the application on September 18, 2000.

WE HEREBY STATE THAT WE HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE.

WE acknowledge the duty to disclose information which is material to the patentability as defined in 37 C.F.R. § 1.56.

WE hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed:

| Application No. | Country | Date of Filing<br>(day/month/year) | Priority Claimed?   |
|-----------------|---------|------------------------------------|---|
| PCT/EP99/01374  | EP      | 03/03/99 ✓                         | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| EP 98104949.7   | EP      | 03/18/98 ✓                         | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
|                 |         |                                    | <input type="checkbox"/> Yes <input type="checkbox"/> No            |

We hereby claim benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

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R/O 16.11.2000 Empfangszeit

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| Application Serial No. | Filing Date |
|------------------------|-------------|
|                        |             |
|                        |             |

We hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112. We acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

| Application Serial No. | Filing Date | Status  |
|------------------------|-------------|---|
|                        |             | <input type="checkbox"/> Patented <input type="checkbox"/> Pending <input type="checkbox"/> Abandoned |
|                        |             | <input type="checkbox"/> Patented <input type="checkbox"/> Pending <input type="checkbox"/> Abandoned |

We hereby appoint the following attorneys and agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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We hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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